REMARKS

Status of Claims

Applicants thank Examiner Burkhart for the consideration given to the present application. Claims 1-26 are currently pending in this application. Claims 7, 12, and 16-26 are withdrawn. Thus, claims 1-6, 8-11, and 13-15 are currently subject to examination.

Claim 5 has been cancelled herein without admission or prejudice. Claim 1 is amended herein to clarify and correct informalities. Support for this amendment is found generally in the original claims and in the Specification as originally filed; for example, support is found in original claim 5 and in the Specification at Page 4, paragraph [0041] (reference being made herein for convenience, to the paragraph numbering of the published application). New claim 27 has been added herein. Support for claim 27 is found generally in the original claims, in the drawings as originally filed, and in the Specification as originally filed; for example, support for claim 27 is found in original claims 1, 6, and 11, in FIG. 1, and in the Specification at paragraph [0062]. Thus, it is believed that no new matter has been entered and entry of the present Amendment is respectfully requested.

Election/Restrictions

The Examiner acknowledged Applicants' election with traverse of Group I in the reply filed on December 13, 2010. However, the Examiner stated that Applicants' arguments were not persuasive asserting that Applicants' references to limitations found in the method claims were not limiting to the vector claims. Thus, the Examiner stated that the requirement is proper and final. Accordingly, the Examiner stated that claims 7, 12 and 16-26 are withdrawn.

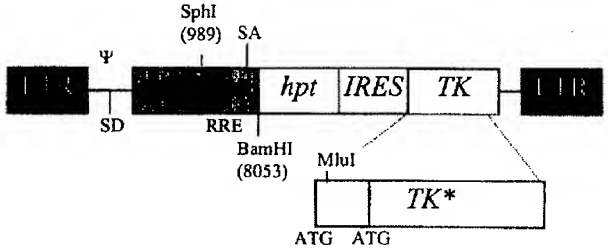
Claim Rejections - 35 U.S.C. §102(b)

The Examiner rejected claims 1-6, 8-10, and 13-15 under 35 U.S.C. §102(b) as being anticipated by Marcello et al. (Res. Vir., 1998).

Applicants respectfully traverse this rejection. Independent claim 1 as amended recites, *inter alia*, a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and the positive selectable marker gene.

Specifically, Applicants submit that Marcello et al. fail to disclose a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and the positive selectable marker gene, as recited in independent claim 1. (Emphasis added). The Examiner asserted that Marcello et al. disclose a replication defective HIV-1 vector comprising deletions in the *gag*, *pol*, and *env* genes. The Examiner also asserted that the vector of Marcello et al. includes hygromycin resistance and herpes virus thymidine kinase genes separated by an IRES sequence, with the HIV LTR as a promoter, citing FIG. 1.

Firstly, Applicants submit that Marcello et al. disclose a vector wherein translation of a thymidine kinase (TK) gene is promoted by an internal ribosome entry site. Marcello et al. disclose that, "[a] replication-defective lentiviral HIV1 vector (HY-IRES-TK) was designed to carry both the hygromycin (Hy) phosphotransferase gene for positive selection and the thymidine kinase (TK) gene of herpes simplex virus driven by the viral long terminal repeat (LTR)." (*See* Summary). Additionally, Marcello et al. disclose that, "[t]he internal ribosome entry site (IRES) from encephalomyocarditis virus was placed between the two genes for their efficient simultaneous translation." (*See* Summary). As depicted in FIG. 1 of Marcello et al., which is provided below for convenience, the structure of the HY-IRES-TK vector includes a thymidine kinase (TK) gene downstream from the IRES. Thus, one of ordinary skill in the art would understand that the expression of the thymidine kinase (TK) gene is driven by the IRES.



Moreover, one of ordinary skill in the art would understand that the use of a positive selectable marker gene downstream of the mutation target gene would require the expression of a fully functional mRNA in order for the cells to survive the presence of a selectable agent (wherein the positive selective marker is a gene whose expression permits the cell to live in the presence of a selectable agent).

Secondly, Applicants submit that the thymidine kinase (TK) gene is not a positive selectable marker gene. The instant Specification discloses that:

> "A positive selective marker is a gene whose expression permits the cell to live in the presence of a selectable agent. The selectable agent is a compound that distinguishes cells that do not express the selectable marker, typically by killing them. Bacterial hygromycin B phosphotransferase (hyg) that confers resistance to the antibiotic hygromycin B and the bacterial xanthine-guanine phosphoribosyl transferase gene (also referred to a the gpt gene) that confers the ability to grow in the presence of mycophenolic acid are examples. Other selectable markers negative in that their use kills cells that do express the protein encoded by the selectable marker and their use is typically in conjunction with a cell line that lacks the relevant activity. Examples of negative selectable markers include the thymidine kinase (tk) gene that is used in conjunction with TK-negative cells." (*See* Page 3, paragraph [0027], emphasis added).

Thus, Applicants submit that thymidine kinase is not a positive selectable marker.

Because the HY-IRES-TK vector of Marcello et al. discloses a thymidine kinase gene downstream of the IRES and thymidine kinase is not a positive selectable marker, Applicants submit that Marcello et al. fail to disclose a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene; and the positive selectable marker gene, as recited in independent claim 1 as amended.

For these reasons, Applicants respectfully request the withdrawal of the rejection of independent claim 1 under 35 U.S.C. §102(b). Additionally, as claim 5 has been cancelled herein without admission or prejudice, and claims 2-4, 6, 8-10, and 13-15 depend from independent claim 1, Applicants also respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. §102(b).

Claim Rejections - 35 U.S.C. §103(a)

The Examiner rejected claims 1-5, 8-11, and 13-15 under 35 U.S.C. §103(a) as being unpatentable over Galipeau et al. (International Pub. No. WO 00/65034) in view of Naldini et al. (PNAS, 1996).

Applicants respectfully traverse this rejection. As previously discussed, independent claim 1 recites as amended, *inter alia*, a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and a positive selectable marker gene. (Emphasis added).

Applicants submit that Galipeau et al. and Naldini et al., singularly or in combination, fail to disclose a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and the positive selectable marker gene, as recited in independent claim 1. The Examiner asserted that Galipeau et al. disclose replication-defective retroviral vectors comprising a CMV promoter driving expression of the HSV-TK and EGFP genes separated by an IRES followed by a retroviral LTR, citing the Abstract and FIGS. 1B and 9B ("pTKiGFP). The Examiner also asserted that EGFP is considered to be a positive marker gene absent any limiting definition of such in the instant Specification, due to the use of EGFP as an expression and infection marker by Galipeau et al.

As previously discussed, the Specification teaches that, "[a] positive selective marker is a gene whose expression permits the cell to live in the presence of a selectable agent," (*see* Page 3, paragraph [0027], emphasis added), and also teaches that, "[t]he selectable agent is a compound that distinguishes cells that do not express the selectable marker, typically by killing them." (*See* Page 3, paragraph [0027], emphasis added). Thus, contrary to the Examiner's assertions, Applicants submit that the Green Fluorescent Protein gene does not fall within the definition of a positive selective marker as set forth in the instant Specification. More particularly, Applicants submit that the Green Fluorescent Protein gene does not permit a cell to live in the presence of a selectable agent, wherein the selectable agent distinguishes cells that do not express Green Fluorescent Protein by killing them. Rather, the Green Fluorescent Protein gene may be used as a reporter gene wherein cells expressing Green Fluorescent Protein exhibit green fluorescence

under blue light. Accordingly, Applicants submit that Galipeau et al. fail to disclose or suggest a lentivirus-based retroviral vector comprising an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and the positive selectable marker gene, as recited in independent claim 1.

Additionally, Naldini et al., which was narrowly cited as disclosing an HIV-1 based vector that is replication-defective via major deletions in the *gag*, *pol*, and *env* genes, fail to cure the deficiencies of Galipeau et al.

Accordingly, all of the cited references, either alone or in combination, fail to disclose or suggest every limitation recited in independent claim 1, and any claim dependent therefrom, as discussed above herein, specifically wherein a lentivirus-based retroviral vector includes an internal ribosome entry site for expression of a positive selectable marker gene, wherein the internal ribosome entry site promotes translation of the positive selectable marker gene, and the positive selectable marker gene. For these reasons, Applicants respectfully request the withdrawal of all rejections under 35 U.S.C. §103(a).

CONCLUSION

It is believed that the above represents a complete response to the Office Action dated March 15, 2011. In light of the foregoing, Applicants respectfully submit that the application is in condition for allowance. It is believed that no additional fees are required, but in the event this is incorrect, the Director is authorized to charge any fees which may be required in connection with the present Amendment, or credit any overpayment, to Deposit Account No. 04-1133. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response. Otherwise, early notification of allowable subject matter is respectfully solicited.

Respectfully submitted,

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